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ON

A STUDY ON HIGH SENSITIVITY CRP AS A SHORT TERM PROGNOSTIC FACTOR IN ACUTE ISCHEMIC STROKE

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CERTIFICATE

This is to certify that this dissertation entitled "A STUDY ON HIGH SENSITIVITY CRP AS A SHORT TERM PROGNOSTIC FACTOR IN ACUTE ISCHEMIC STROKE" **is the bonafide record work done by** Dr. S. APPANDRAJ, **submitted as partial fulfillment for the requirements of M.D. Degree Examinations, General Medicine (Branch I) to be held in March 2008.**

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BRIEF CONTENTS

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List of abbreviations

1.	4S	–	**S**candinavian **S**imvastatin **S**urvival **S**tudy
2.	ACE	–	**A**ngiotensin **C**onverting **E**nzyme
3.	AF	–	**A**trial **F**ibrillation
4.	BMI	–	**B**ody **M**ass **I**ndex
5.	BP	–	**B**lood **P**ressure
6.	CAHD	–	**C**oronary **A**rtery **H**eart **D**isease
7.	CARE	–	**C**holesterol **A**nd **R**ecurrent **E**vents
8.	CBF	–	**C**erebral **B**lood **F**low
9.	CNS	–	**C**entral **N**ervous **S**ystem
10.	CRP	–	**C R**eactive **P**rotein
11.	CT	–	**C**omputed **T**omography
12.	CVD	–	**C**ardio**v**ascular **D**isease
13.	dl	–	**D**eci**l**iter
14.	DM	–	**D**iabetes **M**ellitus
15.	ELISA	–	**E**nzyme **L**inked **I**mmuno ab**S**orbent **A**ssay
16.	FGF	–	**F**ibroblast **G**rowth **F**actor
17.	GM-CSF	–	**G**ranulocyte **M**acrophage **C**olony **S**timulating **F**actor
18.	HDL	–	**H**igh **D**ensity **L**ipoprotein
19.	hs CRP	–	**H**igh **S**ensitivity **C R**eactive **P**rotein
20.	HT	–	**H**yper**t**ension
21.	ICAM	–	**I**nter **C**ellular **A**ddition **M**olecule
22.	Ig	–	**I**mmuno**g**lobulin
23.	IGF	–	**I**nsulin like **G**rowth **F**actor

List of abbreviations

24.	IHD	–	**I**schemic **H**eart **D**isease
25.	IL	–	**I**nter**l**eukin
26.	l	–	**L**itre
27.	LDL	–	**L**ow **D**ensity **L**ipoprotein
28.	LIPID	–	**L**ongterm **I**ntervention with **P**rovastatin in **I**schemic **D**is.
29.	LP(a)	–	**L**ipo**P**rotein (**a**)
30.	MCP-1	–	**M**onocytic **C**hemoattractant **P**rotein – **1**
31.	mg	–	**M**illi**g**ram
32.	MI	–	**M**yocardial **I**nfarction
33.	MONICA	–	**MON**itoring trends and determinants **I**n **CA**rdiovascular disease
34.	MRFIT	–	**M**ultiple **R**isk **F**actor **I**ntervention **T**rial
35.	MRI	–	**M**agnetic **R**esonance **I**maging
36.	NIHSS	–	**N**ational **I**nstitute Of **H**ealth **S**troke **S**cale
37.	PAF	–	**P**latelet **A**ctivating **F**actor
38.	PAI	–	**P**lasminogen **A**ctivator **I**nhibitor
39.	PDGF	–	**P**latelet **D**erived **G**rowth **F**actor
40.	PVD	–	**P**eripheral **V**ascular **D**isease
41.	REC	–	**Rec**oding
42.	RHPP	–	**R**ural **H**ealth **P**romotion **P**roject
43.	SLE	–	**S**ystemic **L**upus **E**rythematoses
44.	TC	–	**T**otal **C**holesterol
45.	tPA	–	**T**issue **P**lasminogen **A**ctivator
46.	VCAM	–	**V**ascular **C**ell **A**dhesion **M**olecule

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ABSTRACT

STUDY OBJECTIVE: To study the hs CRP level in acute ischemic stroke and its association with short term prognosis.

DESIGN AND STUDY: Single centered, Prospective study, Thanjavur Medical College.

PATIENTS: 52 patients admitted within 48 hours of onset of first ischemic stroke were studied.

STUDY PERIOD: Between February 2006 and August 2007.

RESULTS: Following results were obtained,

1. The hs CRP level is increased in all patients after acute ischemic stroke. (Mean hs CRP – 5.94 ± 1.97).
2. The hs CRP level strongly correlates with short term outcome in patients after first ever ischemic stroke. ($p < 0.0005$)
3. The hs CRP level is high in patients with massive infarct in CT brain.
4. The hs CRP level is increased in smokers, obesity, diabetes, hypertension and in post menopausal women.
5. The hs CRP level increases as age advances.
6. TC/HDL ratio, HDL level (<45mg/dl) strongly correlate with short term outcome after acute ischemic stroke. ($p < 0.0005$)
7. TC level (>200mg/dl),diabetic status(FBS>125mg/dl), strongly correlate with short term out come after acute ischemic stroke.($p=0.022$)

CONCLUSION: Patients with stroke had high circulating levels of hs CRP. Short term unfavorable prognosis seems to be associated with elevated hs CRP levels in stroke.

Keywords: stroke, hs-CRP, TC, HDL, Glasgow outcome scale.

CHAPTER - 1 INTRODUCTION

- Introduction

INTRODUCTION

Acute ischemic stroke develops as a result of sudden interruption in the focal cerebral blood flow[31,88].

The cause of the stroke is an embolic or thrombotic occlusion in 70-80% of patients with severe symptoms[23,87].

Recent research has shown that an inflammatory reaction is triggered within the hour in the brain tissue injured by an ischemic stroke and continues in the days following the appearance of symptoms and that this reaction contributes to neuronal damage[13].

Increased CRP levels are accepted as a sensitive but non specific marker of the acute inflammatory conditions[50].

Laboratory and experimental findings have shown that atherosclerosis is a reflection of a chronic inflammatory process in addition to lipid deposition[56,70]. Inflammatory mechanisms have been

known to play a role in all stages of atherosclerosis, from initiation to development[7,52,74,75].

It has been reported that it is possible to use the increase in the concentration of acute phase reactants and especially the high sensitivity C- Reactive proteins (hs CRP) to help predict future cardiovascular mortality[37,52,70,73]. Various prospective studies have found initial CRP levels to be higher in persons who develop stroke, IHD, peripheral artery disease[54,60].

Among all neurological disorder of adult life, CVA clearly rank first in frequency and importance posing a major socio economic challenge in occupational neuro rehabilitational programmes of stroke survivors.

Identification of risk factors and its interactions with other precursors may yield important clues concerning pathogenesis and thereby led to stroke prevention.

Our study was done in Thanjavur Medical College that caters population from SIX nearby districts.

CHAPTER - 2 AIM OF THE STUDY

- Aim of the study

Aim of the study

1. To determine the hs CRP level following acute ischemic stroke and its association with short term prognosis.

2. To correlate the level of hs CRP with severity of acute ischemic stroke.

3. To study the relationship of hs CRP level with various known risk factors of ischemic stroke.

CHAPTER - 3 REVIEW OF LITERATURE

- Definition of Stroke
- Epidemiology
- Pathophysiology of Stroke
- Pathophysiology of Ischemic Stroke
- Risk Factors
- Inflammation Endothelial dysfunction and Atherogenesis
- Risk factors and mechanism of injury
- CRP as a predictor of stroke risk
- **Stroke scales**

Review Of Literature

3.1 DEFINITION OF STROKE:

Stroke by definition is a syndrome of rapidly developing clinical signs of focal disturbance of cerebral function with symptoms lasting 24 hours or longer or leading to death with no apparent cause other than vascular origin.

3.2 EPIDEMIOLOGY:

3.2.1 WORLD:

Each year stroke affects 15,000,000 people worldwide, two thirds of whom die or are left permanently disabled [40]. In 1990 more than 38,000,000 disability adjusted life years were lost worldwide due to stroke; this disease burden is projected to increase to 61,000,000 disability adjusted life years by 2020.

3.2.2 INDIA:

Based on retrospective analyses of subjects admitted in urban hospitals in India it was found that stroke constitutes nearly 2% of all hospital cases and 20% of neurological admissions.

3.3 PATHOPHYSIOLOGY OF STROKE:

One of the three mechanisms is usual.

(1) Arterial embolism from distant site usually the carotid, vertebral or basilar arteries and subsequent brain infarction.

(2) Arterial thrombosis causing occlusion in atheromatous carotid, vertebral artery with subsequent brain infarction.

(3) Hemorrhage into the brain (intracerebral or subarachnoid).

Less commonly,

- Venous infarction
- Carotid or vertebral artery dissection
- Polycythemia
- Fat and air embolism
- Multiple sclerosis
- Mass lesions
- Very rarely arteritis, neurosyphilis, SLE, and mitochondrial disease.

3.4 PATHOPHYSIOLOGY OF ISCHEMIC STROKE:

A fall in cerebral blood flow to zero causes death of brain tissue within 4-10 min.

CBF <16 to 18 ml/100gm tissue per min cause infarction within an hour. Values <20 ml/100gm tissue per min cause ischemia without infarction unless prolonged for several hours or days. There is a loss of neuronal electrical function which is reversible stage.

When blood flow decreases to 10 ml/100gm/min then aerobic mitochondrial metabolism fails and anaerobic metabolism leads to lactic acidosis. As a sequel to this, sodium and water reenter the cell and potassium leaks out of the cell due to failure of energy dependant intracellular homeostasis leading to irreversible cell death.

Based on these facts, concept of ischemic penumbra was formulated. It is an area of brain that has reached the reversible stage of electrical failure, but has not yet passed into irreversible stage. Thrombolytic agents are used in this time window to salvage the ischemic penumbra zone.

3.5 RISK FACTORS:

NON MODIFIABLE:

- Age (increases with age)
- Gender (males > females)
- Hereditary / familial factor
- Race/ ethnicity.

MODIFIABLE RISK FACTORS: (**Table 3.1**)

RISK FACTOR	INTERVENTION	REDUCTION IN ISCHEMIC STROKE RISK
• Hypertension	• Treat	• + +
• Smoking	• Stop	• + +
• Lifestyle	• More active	• +
• Alcohol	• Moderate intake	• +
• Hypercholesterolemia	• Statin therapy	• +
• Raised haematocrit	• Reduce	• +
• Atrial fibrillation	• Anticoagulate	• +
• Sleep apnoea	• Treat	• +
• Obesity	• Wt reduction	• Probable
• Diabetes	• Good control	• Probable
• Carotid artery stenosis	• Surgery	• + +

+ +, Major correlation with reduced risk, +, moderate correlation with reduced risk. Ref : Clinical Medicine.,Kumar and clark.,6th ed.,

3.6 INFLAMMATION, ENDOTHELIAL DYSFUNCTION ATHEROGENESIS:

Atherogenesis is itself an inflammatory process. When endothelium is physically challenged or becomes dysfunction , a cascade of events precipitated initiating a cycle of injury , immunological induction and amplification.

Causes of endothelial dysfunction include sheer stress related to hypertension, oxidized LDL , homocysteine, and smoking . Dysfunctional endothelium leads to increased permeability to lipoprotein and upregulation of leucocyte and endothelial adhesion molecules.

In response to the presence of certain activating substances including oxidized LDL , monocytic chemoattractant protein (mcp-1) , interleukin IL-8 and PDGF leukocytes migrate into the wall of the artery.

Induced by oxidized LDL , mcp-1 promotes diapedesis of monocytes across the endothelium . Granulocytic macrophage colony-stimulating factor transforms monocytes into macrophages, which elaborate tumour necrosis factor-ά (TNF-ά) , IL-1 , proteolytic enzymes

including matrix metalloproteinases and growth factors including PDGF , insulin like growth factor (IGF) .

These macrophages in addition to smooth muscle , activate T cells by presenting antigens including oxidized LDL . Other trophic factors such as IL-2 , TNF-ά, and GM-CSF cause activated Tcells to produce INF-ά, TNF-ά, and TNF-β leading to stimulation of macrophages and further upregulation of leukocyte adhesion molecules . This feedback amplifies cycle of inflammation.

Regulation of adhesion molecules also is influenced by mechanical forces. Low sheer stress upregulates expression of vascular cell adhesion molecule (VCAM-1) , why increased sheer stress can lead to increased gene expression of intercellular adhesion molecule (ICAM-1), VCAM-1, and PDGF-β. ICAM-1, VCAM-1, are members of an immunoglobulin super family whose members have both a transmembrane region and a cytoplasmic tail. They are expressed on endothelial cells and bind to integrins CD11a/CD18 and VLA-4 respectively. CD11a/CD18 are found in neutrophils monocytes macrophages and lymphocytes while VLA-4 is found on Monocytes and lymphocytes.

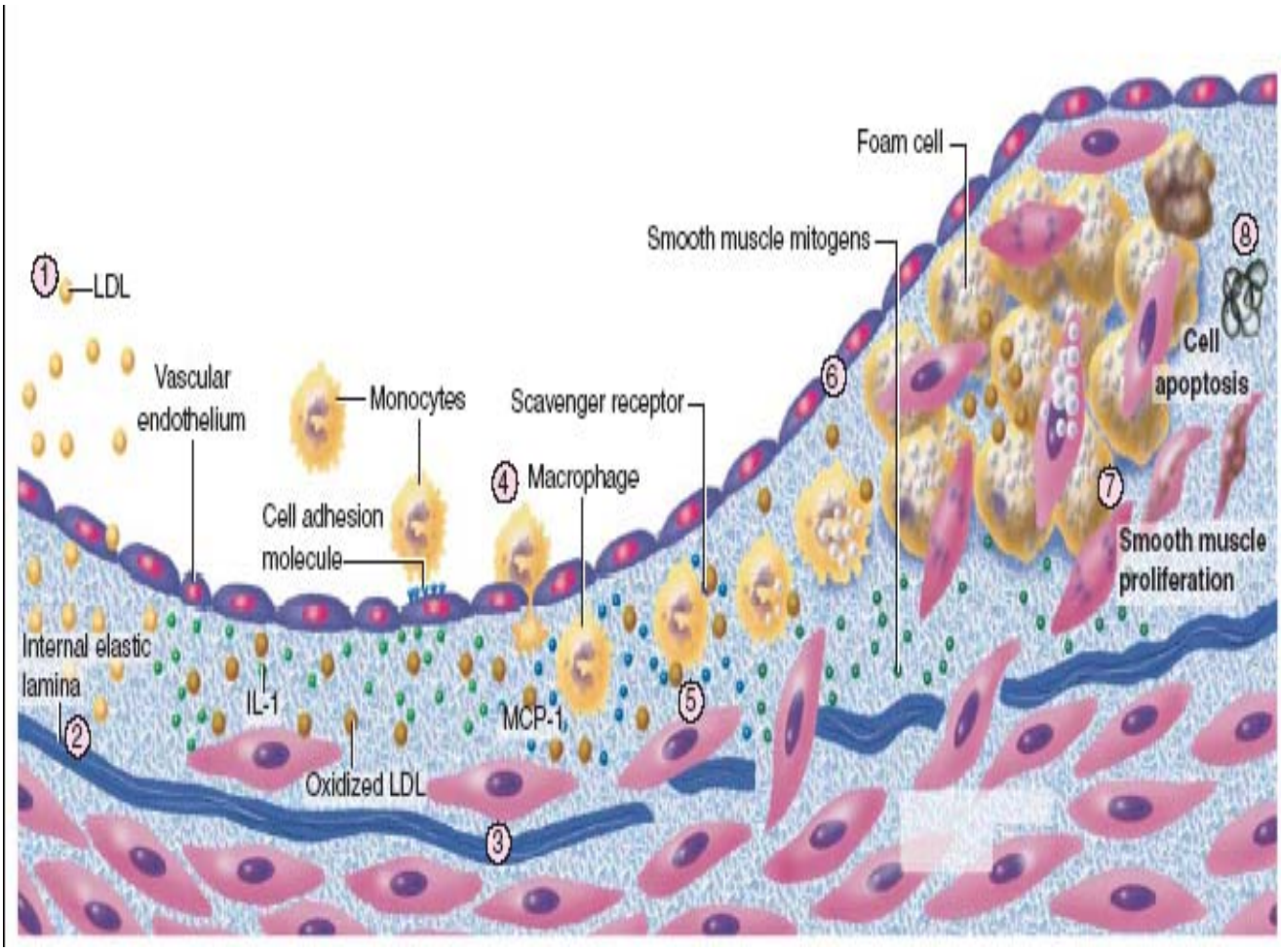

Fig-3.1 Inflammation and Atherosclerosis

Platelets attach to dysfunctional endothelium, macrophages, and expose collagen. The activated platelets release granules containing cytokines and growth factor, causing conversion of arachidonic acid to both thromboxane A2 leading to further platelet aggregation and leukocyte , there by amplifying the inflammatory process. Platelets also can be activated by PAF (platelet activating factor) produced by monocytes, endothelial cells and neutrophils. PAF causes platelet aggregation and degranulation and also promote leukocyte activation.

To summarize the process of plaque formation initiate with one or more injurious factors. The resultant inflammatory cascade leads to incorporation of oxidized LDL into macrophages forming foam cells, which together with T cells, make fatty streaks. Next PDGF, TGF-β , FGF-2 act to cause smooth muscle migration to the site . Next increased activity of specific chemokines and cytokines leads to the formation of fibrous cap on top of necrotic core of lipid , leukocytes and debris. The continued presence of macrophages producing metaloproteinases and other proteolytic enzymes cause thinning of fibrous cap and priming it for ulceration and rupture.

Importantly, the recognition of the importance of the inflammatory milieu within atherosclerotic plaque in precipitating plaque erosion and

rupture leading to events has redirected attention away from the focus solely on the degree of stenosis in the arterial tree. Most acute myocardial infarctions, for example, occur in patients with substenotic lesions. According to the current model of atherosclerosis, initial plaque formation is abluminal, or external to the lumen, and is angiographically silent. Newer techniques such as intravascular ultrasound (Raggi, 2005) or contrast-enhanced carotid MRI[86] can detect abnormal and active plaque even in the absence of stenosis.

Although established as the cause of coronary artery occlusion, and as a possible final mechanism of extracranial carotid artery occlusion, this ulceration/rupture is not typical of intracranial arterial occlusion[38]. Although atherosclerotic lesions in different vascular beds share many characteristics, mechanisms related to symptomatic conversion are likely site-specific. Most stroke risk are associated with carotid stenosis.

Recent evidence implies that the risk of clinical events is related not only to local factors within the atherosclerotic plaque, such as the state of the necrotic core or the fibrous cap, but also to blood-borne, or systemic factors[39]. Thus, circulating levels of cytokines, prothrombotic factors or acute-phase reactants may play a role in precipitating acute stroke in the setting of diseased but not stenotic vessels. For example, evidence exists

that markers such as CD40 ligand and CRP predict progression of atherosclerosis and risk of stroke[49].

3.7 Risk factors and mechanism of injury:

3.7.1 Hypertension:

Hypertension confers a relative risk for stroke of 3- to 5-fold[6]. It continues to represent a significant public health risk. Recently, even high-normal blood pressures, 130-139/85-89 mm Hg, have been shown to be associated with elevated cardiovascular risk[84]. Hypertension can result in mechanical injury to endothelium through increased sheer stress, thereby increasing the number of endothelial adhesion molecules, which attract monocytes and lymphocytes.

Overactivity of the renin-angiotensin system has been implicated in the progression of atherosclerosis. Angiotensin II, in addition to being a potent vasoconstrictor, can lead to smooth muscle hypertrophy, extracellular matrix production, and induction of cytokines. Expression of angiotensin-converting enzyme (ACE) has been demonstrated in macrophages, lymphocytes, and microvessels neighboring carotid plaques[21].

This suggests a role for ACE inhibitors as part of a prophylactic regimen for stroke. One study showed that patients with vascular disease who were treated with the ACE inhibitor ramipril had a lower stroke rate than patients treated with placebo[82] (Heart Outcomes Prevention Evaluation Study investigators). Additionally, a substudy evaluating plaque progression using ultrasound suggested that ramipril also may retard atherosclerotic progression (Lonn et al, 2001).

Independent of the effects of angiotensin II, hypertension has been shown in animals to increase formation of hydrogen peroxide and free radicals, which in turn can increase leukocyte adhesion[74,79]. Thus, additional pathophysiologic studies are needed.

3.7.2 Low-density lipoprotein:

Oxidized LDL is a relatively active form of LDL, which attracts monocytes, increases adherence of monocytes, induces conversion of monocytes to macrophages, and decreases the motility of macrophages. While native LDL cannot be incorporated into a macrophage or smooth muscle cell, oxidized LDL can be taken up by scavenger receptor A (SRA), allowing for formation of foam cells. High plasma levels of LDL increase

the entry rate of LDL into the intima. Serum high-density lipoprotein (HDL) exerts a protective effect by deterring LDL peroxidation.

Macrophages, smooth muscle cells, and endothelial cells can oxidize LDL. This leads to a spectrum of variably oxidized LDLs with a heterogeneity of deleterious effects. In culture, oxidized LDL is toxic to endothelial cells. Studies have shown the presence of oxidized LDL at sites of inflammation, raising a potential mechanism by which areas of inflammation may promote atherogenesis at remote sites.

Several studies support a role for beta-hydroxy beta-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (ie, statins) in slowing the progression of intima media thickness, a frequently used surrogate for carotid atherosclerosis[22] (Crouse, 1995). Lowering of LDL has also been associated with reduction in plaque progression in studies using intravascular ultrasound[48].

Table 3.2 – Secondary Prevention Trials of Statin Therapy

	4S	CARE	LIPID
Duration(yrs)	5.4	5	6.1
Intervention	Simvastatin, 10-40 mg/day	Pravastatin, 40mg/day	Pravastatin, 40mg/day
% LDL change	-36	-28	-25
% change in stroke risk	-30	-31	-19

3.7.3 Diabetes mellitus :

Diabetes mellitus (DM) increases stroke risk by 1.5- to 3-fold. Not only does DM increase the risk of stroke, it also increases the rate of mortality from stroke. DM accelerates atherosclerosis and induces both microangiopathic changes and large-vessel atherosclerosis. Long-standing DM is associated with endothelial dysfunction, including reduction in endothelium-mediated vasodilator production. Additionally, acute hyperglycemia has been demonstrated to impair cerebrovascular reactivity mediated, at least in part, by endothelial production of nitric oxide and prostaglandins[10].

3.7.4 Smoking :

Smoking represents a significant and modifiable risk factor. It almost doubles the risk of stroke. This is thought to occur by multiple mechanisms. Smoking leads to decreased arterial wall compliance, increased platelet aggregation, increased fibrinogen levels, and decreased HDL cholesterol levels.

A small study recently showed that smokers had lower production of endogenous tissue plasminogen activator (tPA) antigen induced by substance P infusion, suggesting an impairment of endogenous fibrinolysis in smokers (46).Endogenous tPA can be released by endothelial cells to lyse subclinical clots, which may exist on denuded areas on the surface of atherosclerotic plaques.

3.7.5 INFECTION :

In light of the increasing acceptance of atherosclerosis as a chronic inflammatory disease, it has been hypothesized that acute and chronic infections may play a role in vascular disease. Increased leukocyte counts are associated in observational studies with carotid thickness[17] and aortic arch plaque thickness[19] in some populations as well as with clinical stroke[18]. In a clinical trial in which leukocyte levels were followed

repeatedly over time, evidence suggested that those patients who had recurrent clinical events were more likely to have had recent elevations in their leukocyte counts[26]. These findings indirectly implicate infection in the pathogenesis of plaque formation and stroke risk.

Several studies provide evidence that patients with stroke are more likely than control subjects to have had an upper respiratory infection within the previous 2 weeks[25] (Bova, 1996). This suggests a plausible role for infection in the conversion of an asymptomatic to a symptomatic plaque.

3.7.6 Chlamydia :

C pneumoniae is the infectious pathogen that has been most extensively studied in relation to atherosclerosis and stroke. The presence of C pneumoniae in the intima, media, macrophages, and smooth muscle of some carotid endarterectomy specimens is evident. Detection of C pneumoniae in serum, however, correlates poorly with its detection in carotid plaques (LaBiche, 2001).

Evidence also exists that patients with coronary disease[33] and stroke[18] are significantly more likely than control subjects to have elevated levels of immunoglobulin G (IgG) or immunoglobulin A (IgA) against C

pneumoniae. However, prospective studies have not always confirmed these findings[33].

In an animal study, inoculation with C pneumoniae increases atherosclerosis, and azithromycin attenuates this effect[43]. Facilitates conversion of macrophages to foam cells; increases the oxidation of LDL. Hypersensitivity to heat stroke proteins also play a role.

3.8 Inflammatory Biomarkers As Predictors of Stroke Risk:

♣ Of all inflammatory biomarkers C reactive protein is most extensively studied.

3.8.1 CRP:

CRP is an acute phase reactant and a component of innate immunity, increases in response to inflammatory stimuli and is a known mediator of complement activity, adhesion molecule production, and chemokine and thrombogenic factor release.

The physiological function of CRP is to induce non specific defense mechanism to scavenge altered lipoproteins.

In the past CRP was used only as acute phase protein with cut off values between 0.5 and 1.0 mg / dl.

Conventional nephelometric and turbidimetric tests allow the measurement of concentrations of 0.2 to 0.4 mg/ dl with sufficient precision. ELISAs developed for research purposes gave the first indication that most healthy persons have a CRP concentration far below these cut off values and that higher values are associated with an elevated cardiovascular risk[59].

Later very sensitive commercial tests were developed using mostly particle enhanced nephelometry or turbidiometry, where the sensitivity is 0.02 mg/ dl. These new tests are called high sensitivity C reactive protein (hs CRP).

CRP is produced by liver, vascular smooth muscle cells and adipocytes. It is a stable protein not affected by freezing and thawing cycles in large epidemiological studies. It has little diurnal variation and can be measured in non fasting state.

The hs CRP, therefore qualifies as a good reproducible assay and currently widely available.

But CRP is non specific. Increase in levels occur in acute infections and inflammation such as lymphoma, lupus, giant cell arteritis, rheumatoid arthritis, inflammatory bowel disease, osteomyelitis.

3.8.2 CRP – As a Predictor of CVD:

Increase in hs CRP levels are independent predictor of risk of recurrent myocardial infarction, stroke, peripheral arterial disease and sudden cardiac death[3,20,66].

Studies reveal that highest quartile for CRP compared with the lowest quartile was associated with age adjusted relative risk of first ischemic stroke and transient ischemic stroke of 2.0 for men and 2.7 for women[75].

CRP adds to the predictive value of Framingham risk score[3] and to the vascular risk associated with the metabolic syndrome[66].

CRP levels showed statistically significant positive correlations with other established risk factors including age, number of cigarettes smoked per day, body mass index, systolic and diastolic pressure, total cholesterol,

triglycerides, homocysteine, fibrinogen and d-dimers. CRP levels correlated inversely with HDL – C[71].

When multi variate analysis was performed to control for these associations CRP emerged as a independent risk factor in its own right.

Hs CRP was the only inflammatory risk factor that independently predicted risk and the inclusion of hs CRP improved the predictive ability of the models over those containing lipid values alone ($p < 0.001$) in several studies. (Ridker).

The addition of CRP to other CVD risk factors increased the over all predictive value. When CRP and TC : HDL ratio were used together, there is improvement in risk assessment[64].

The role of hs CRP and other inflammatory markers has prognostic indicators after first stroke has been investigated in many studies[15].

Hs CRP predicts mortality after stroke[14,45]. Elevated hs CRP levels in patients with stroke is associated with short term unfavorable prognosis[80].

Patients with the highest CRP quartile experienced reduction in MI compared to lowest quartile on aspirin therapy. Helps to identify persons who benefit from aspirin therapy.

CRP levels were reduced by lipid lowering drug PRAVASTATIN showing that CRP is a modifiable risk factor and suggesting that an anti inflammatory activity may contribute to the drugs therapeutic efficacy[51].

Table 3.3 Prospective studies of CRP as a Risk Factor for Future Cardiovascular Disease:

Study	End point	Relative risk*
Physician's Health Study[59,60]	MI STROKE PVD	2.9 1.9 2.1
Women's Health Study[62]	CVD	4.4
MRFIT[37]	CHD Death	4.3
CHS/RHPP[83]	CHD	2.3
MONICA[36]	CHD	2.7
Helsinki Heart Study[72]	CHD	3.6

* **Upper vs Lower Quartile**

Table3.4 Reference Values of hs CRP:

Interpretation	CRP (mg/L)
Low cardiac risk	<1.0
Average cardiac risk	1.0 - 3.0
High cardiac risk	>3.0
Infection or Inflammation	>10

Table 3.5 Clinical Utility of Novel Markers in CVD Risk:

Marker	Assay conditions standardized?	Prospective studies consistent?	Additive to TC and HDL ?	Additive to Framingham Risk ?
Lipoprotein(a)	-	+/-	+/-	-
Homocysteine	+	+	+/-	-
tPA & PAI-1	+/-	+	+/-	-
Hs CRP	+	+	+	+

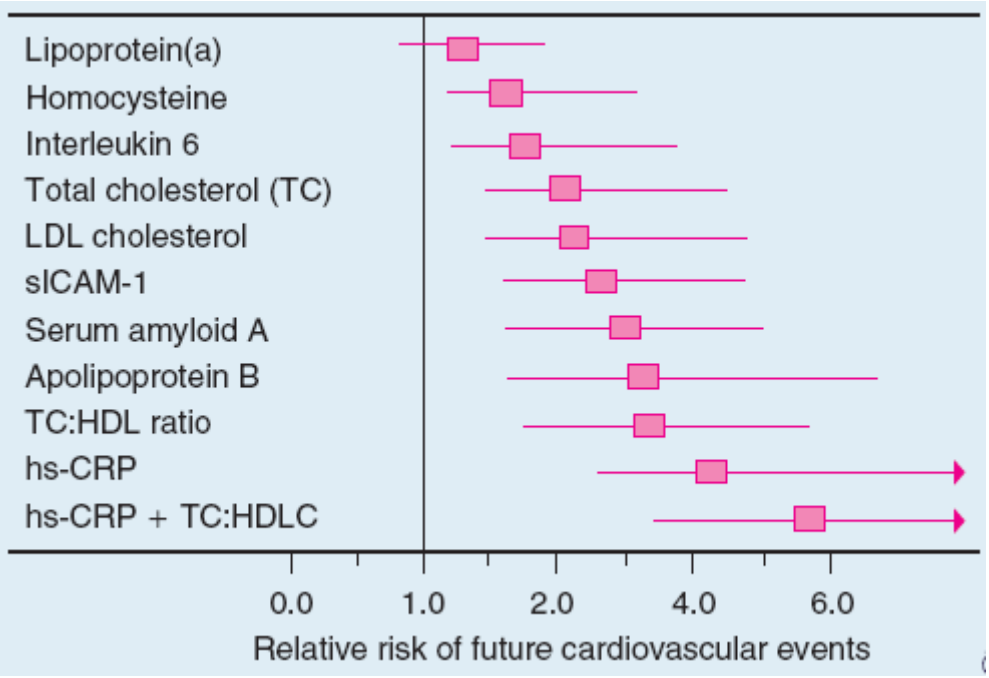

Figure-3.2 : Relative risk of future cardiovascular events

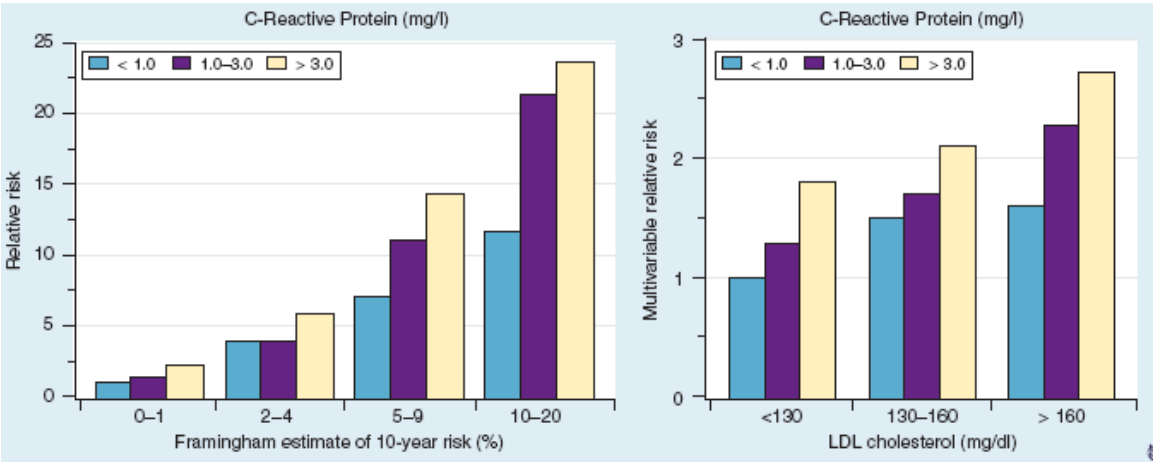

Figure-3.3 : CRP level and relative risk of CVD

3.9 Stroke Scales:

Some stroke scales used to assess functional outcome are,

1. Glasgow outcome scale
2. Barthel index
3. Modified Rankin scale
4. NIH Stroke scale
5. Stroke impact scale
6. AHA Stroke out come classification
7. Scandinavian stroke scale
8. Orgogozo stroke scale
9. Canadian stroke scale.

CHAPTER - 4 MATERIALS AND METHODS

- Setting
- Study design
- Study method
- Hs CRP Test
- Assessing functional outcome

4 Materials and methods

4.1 **Setting:** MEDICAL WARDS, THANJAVUR MEDICAL COLLEGE.

4.2 **Study design:**

This study is single centered prospective study carried out in department of medicine of thanjavur medical college during the period of February 2006- August 2007. Total number of patients included in the study were 52. The detailed history regarding the risk factors like diabetes, coronary artery disease, hypertension, hyperlipedemia, smoking, and alcohol use were elicited from the patient. Standard approved protocol was used for all patients.

4.2.1 Inclusion criteria:

1. Age 41-85.
2. First acute ischemic stroke were included
3. Only ischemic stroke patients confirmed by CT brain were included.
4. Patients who got admitted within 48 hrs of stroke onset were included.

4.2.2 Exclusion criteria:

1. Other than ischemic stroke were excluded.
2. Patients admitted after 48 hrs of stroke onset were excluded.
3. Age less than 40 yrs and greater than 85 were excluded.
4. Patients with lymphoma, lupus, rheumatoid arthritis , osteomyelitis, malignancy, other connective tissue diseases were excluded.
5. Recent infection , trauma or surgery within a month were excluded.
6. Patients with valvular heart disease, atrial fibrillation, thyroid disease, renal disturbance were excluded.
7. Patients with previous history of stroke , TIA , RIND were excluded.
8. Acute myocardial infarction were excluded.

*4.*3 Study Method:

4.3.1 Clinical Examination:

All patients were examined for hypertension, obesity, carotid artery thrill and bruit. A detailed cardiovascular and CNS examination were performed and the findings were recorded. ECG and Chest X Ray PA view

were taken to rule out AF and valvular heart disease as well as acute MI. BP at the time of admission were recorded and BMI were calculated . Patients with BMI>30 were labeled as obese.

4.3.2 Investigations:

1. Hb%.
2. Total count, differential count.
3. Random blood sugar, urea , creatinine.
4. Fasting total cholesterol(TC), Fasting high density lipoprotein cholesterol(HDL-C).
5. CT brain plain at the time of admission.
6. Hs CRP test was done within 24-48 hours of stroke onset.

4.4 Hs-CRP test:

Specimen: serum or heparinised or EDTA plasma.

Volume: 0.5 – 1.0 ml.

Storage: Refrigerate for maximum 8 days. May be frozen at -25˚C or lower if samples are frozen within 24 hrs after collection. Repeated freeze thaw cycles to be avoided.

Method: Nephelometric method utilizing latex particles coated with CRP monoclonal antibodies.

4.4.1 Principle of nephelometry:

When light is passed through a turbid solution, light rays strike the particles in the solution and change their direction of movement. This phenomenon is called scattering. Size, concentration, and shape of molecules altogether determine the amount of scattered light. Size and shape determines the angle of scatter and concentration intensifies the scattered light at the particular angle. The liquid sample is exposed to the beam of light rays in a transparent holder. The rays get scattered and a detector kept at right angle of the light path detects the intensity of the rays at that angle. This is further quantified by rehearsing the phenomena with known molecule at known concentration that is using a standard. Polystyrene particles coated with the antibodies are agglutinated when mixed with the samples containing the test parameter.

4.4.2 Instrument: BN-100 FROM DADE BEHRING , USA.

ADVANTAGES:

1. Fully automatic and rapid quantititative determination.
2. Fast with kinetic method. Results in few minutes.
3. Can perform 100 tests per hour.
4. Sensitivity- 0.1 mg/l.

4.5 Assessing Functional Outcome:

♣ On seventh day patients clinical and functional status were assessed using GLASGOW OUTCOME SCALE.

GLASGOW OUTCOME SCALE:

Note: The scale presented here is based on the original article by Jennett and Bond.

SCORE	DESCRIPTION
1	**Death**
2	**Persistent vegetative state** Patient exhibits no obvious cortical function.
3	**Severe Disability** (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both
4	**Moderate Disability** (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	**Good Recovery** Resumption of normal activities even though there may be minor neurological or psychological deficits.

References

**Jennett B, Bond M. "Assessment of outcome after severe brain damage."
Lancet 1975 Mar 1;1(7905):480-4**

CHAPTER - 5 RESULTS AND OBSERVATIONS

- Study results and observations

Results and observation

5.1 Age:

Patients of age > 40 yrs and < 85 yrs were included in this study.

- Total no of patients – 52
- Mean age of patients – 60.3 yrs
- Standard deviation – 10.5 yrs
- Range – 37
- Maximum age – 80 yrs
- Minimum age – 43 yrs

5.2 Frequency tables:

Table 5.1 : Sex

SEX

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	MALE	39	75.0	75.0	75.0
	FEMALE	13	25.0	25.0	100.0
	Total	52	100.0	100.0	

- 75 % of patients were males.

Table 5.2 : Smoking

SMOKING

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	30	57.7	57.7	57.7
	NO	22	42.3	42.3	100.0
	Total	52	100.0	100.0	

- 57.7 % of this study group were smokers who smokes more than one packet per day

Table 5.3 : Alcohol

ALCOHOL

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	8	15.4	15.4	15.4
	NO	44	84.6	84.6	100.0
	Total	52	100.0	100.0	

- Those who take more than three drinks per day were included.
- 15% of patients were alcoholics.

Table 5.4 : Diabetes mellitus

D.M.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	12	23.1	23.1	23.1
	NO	40	76.9	76.9	100.0
	Total	52	100.0	100.0	

- All patients who were on regular or irregular treatment included.
- 23% were diabetics in this study.

Table 5.5 : Hypertension

H.T

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	30	57.7	57.7	57.7
	NO	22	42.3	42.3	100.0
	Total	52	100.0	100.0	

- Patients who had BP> 140/90 at the time of admission were included.
- 57.7% found to have high BP.

Table 5.6 : CAHD

CAHD

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	4	7.7	7.7	7.7
	NO	48	92.3	92.3	100.0
	Total	52	100.0	100.0	

- Only 8% had previous history of CAHD.

Table 5.7 : Obesity

OBESITY

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	5	9.6	9.6	9.6
	NO	47	90.4	90.4	100.0
	Total	52	100.0	100.0	

- Only 10% were obese in this study.

Table 5.8 : Total Cholesterol

TCL REC

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	< 200	37	71.2	71.2	71.2
	> 200	15	28.8	28.8	100.0
	Total	52	100.0	100.0	

- 71% patients had TC<200 mg/dl.
- Mean TC 189.6 ± 16.9 ; Median TC 190 ; Range 60

Table 5.9 : High Density Lipoprotein

HDLREC

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	> 45	11	21.2	21.2	21.2
	<45	41	78.8	78.8	100.0
	Total	52	100.0	100.0	

- In this study only 22% had HDL >45mg/dl.
- Mean HDL 41.08 ± 3.07 ; Median HDL 41 ; Range 11

Table 5.10 : TC/HDL Ratio

TCL /HDL RATIO

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	< 4	9	17.3	17.3	17.3
	>4	43	82.7	82.7	100.0
	Total	52	100.0	100.0	

- Ideally it should be less than 4.
- Mean TC/HDL 4.64 ± 0.6 ; Median TC/HDL 4.64 ; Range 2.3
- In this study only 17 % had TC/HDL < 4

Table 5.11 : CRP Distribution

CRP DISTRIBUTION

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	2-3	5	9.6	9.6	9.6
	3-4	5	9.6	9.6	19.2
	4-5	7	13.5	13.5	32.7
	5-6	7	13.5	13.5	46.2
	6-7	13	25.0	25.0	71.2
	7-8	7	13.5	13.5	84.6
	8-9	4	7.7	7.7	92.3
	9-10	3	5.8	5.8	98.1
	10-11	1	1.9	1.9	100.0
	Total	52	100.0	100.0	

- Mean hs CRP of all patients 5.94 ± 1.97 ; Median 6.15 ; Range 8.0
- Maximum value – 10.1mg/l ; Minimum – 2.1mg/l

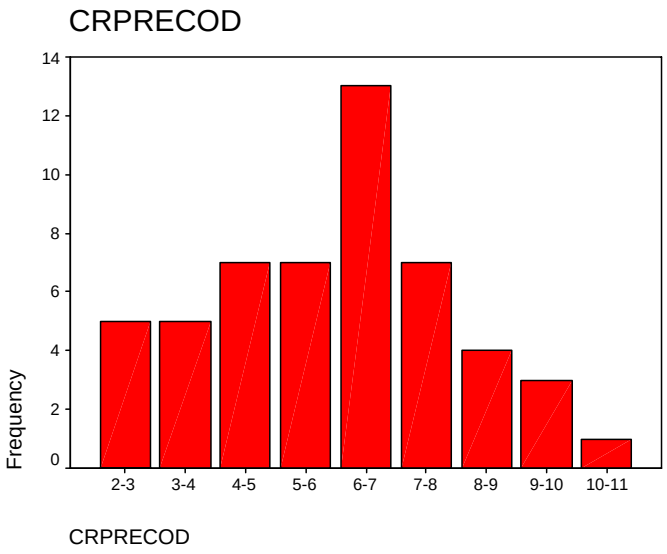

Figure 5.1 : CRP Distribution

- It shows >94 % of patients had hs CRP > 3mg/l
- It shows clearly that hs CRP levels are increased in stroke

Table 5.12 : Glasgow Outcome Scale

GLASGOW SCALE REC

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	DEATH	4	7.7	7.7	7.7
	VEG / SEVERE DIS	32	61.5	61.5	69.2
	MILD/ GOOD	16	30.8	30.8	100.0
	Total	52	100.0	100.0	

- 70 % had poor prognosis
- 7.7 % mortality was noted in these patients
- Only 30 % had good recovery

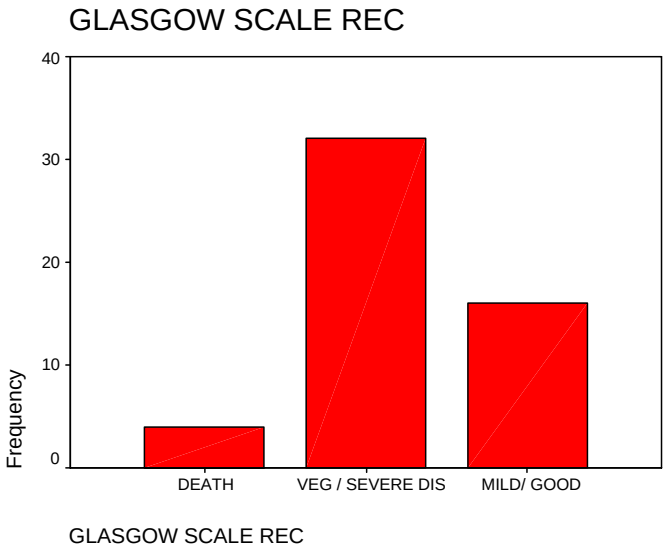

Figure 5.2 : Glasgow Outcome Scale

- Patients with score of 2 and 3 were unable to walk
- Patients with score of 4 and 5 were able to walk

5.3 RISK FACTOR COMPARISON WITH GLASGOW OUTCOME SCALE :

5.3.1 Hs CRP level and functional outcome :

Table 5.13 : GLASGOW SCALE REC * CRPRECOD

Crosstab

Count

		CRPRECOD									
		2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11	Total
GLASGOW SCALE REC	DEATH				1				2	1	4
	VEG / SEVERE DIS			3	4	13	7	4	1		32
	MILD/ GOOD	5	5	4	2						16
Total		5	5	7	7	13	7	4	3	1	52

P < 0.0005 (Statistically significant)

- Mean hs CRP of all 52 patients 5.94 ± 1.96mg/l
- Mean hs CRP of all patients who died during study 8.85 ± 1.98mg/l
- Mean hs CRP of all patients who were unable to walk (patients in GOS score of 2 and 3) is 6.68 ± 1.1mg/l
- Mean hs CRP of patients who were able to walk (patients in GOS score of 4 and 5) is 3.73 ± 1.1mg/l
- Total no of patients who had massive infarct in CT Brain – 9
- Mean hs CRP who had massive infarct is 8.7 ± 0.96mg/l
- Total no of patients who had lacunar infarct – 10
- Mean hs CRP of patients who had lacunar infarct is 3.27 ± 0.93mg/l
- Applying chi square test for association between hs CRP levels and GOS, p < 0.0005 which is statistically significant
- All these data clearly showed high hs CRP levels following acute ischemic stroke indicates poor outcome.

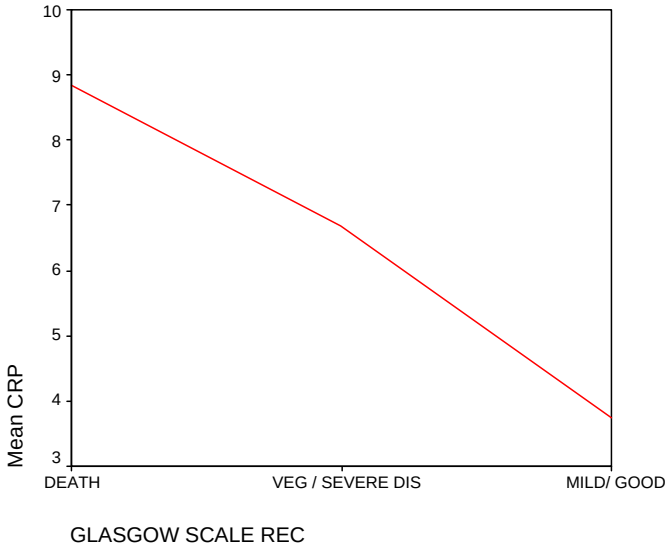

Figure 5.3 : GLASGOW SCALE REC * CRPRECOD

- Above graph shows when hs CRP increases, worse is the prognosis.

5.3.2 Total cholesterol and functional outcome:

Table 5.14 : GLASGOW SCALE REC * TCL REC

Crosstab

Count

		TCL REC		
		< 200	> 200	Total
GLASGOW SCALE REC	DEATH	1	3	4
	VEG / SEVERE DIS	21	11	32
	MILD/ GOOD	15	1	16
Total		37	15	52

P = 0.014 (Statistically significant)

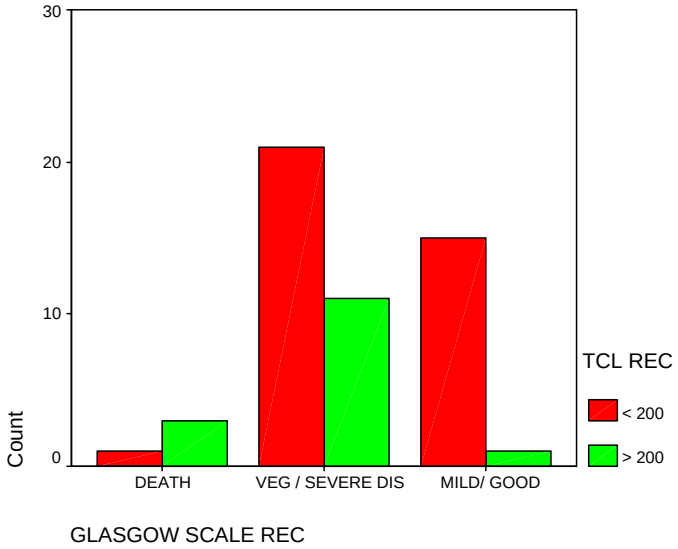

Figure 5.4 : Glasgow Scale REC*TC

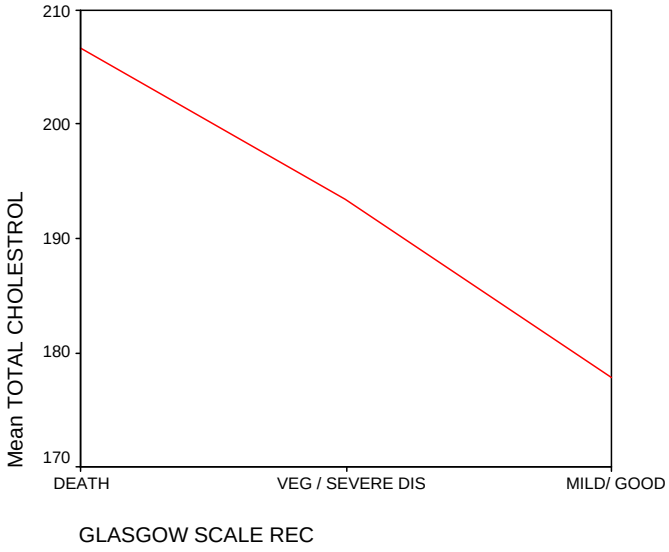

Figure 5.5 : Glasgow Scale REC*TC(Graph)

- 75 % of patients who died had TC > 200mg/dl
- 34 % of patients who were unable to walk had TC > 200mg/dl
- Only 6 % of patients who were able to walk had TC > 200mg/dl.
- Applying chi square test p = 0.014 statistically significant

5.3.3 HDL and functional outcome :

Table 5.15 : GLASGOW SCALE REC * HDLREC

Crosstab

Count

		HDLREC		
		> 45	<45	Total
GLASGOW SCALE REC	DEATH	1	3	4
	VEG / SEVERE DIS	1	31	32
	MILD/ GOOD	9	7	16
Total		11	41	52

P < 0.0005 (Statistically significant)

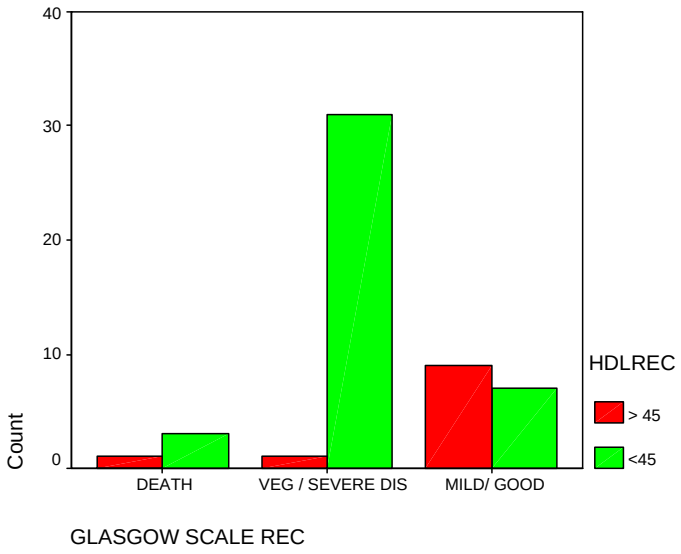

Figure 5.6 : Glasgow Scale REC* HDL REC

- 56 % of patients who were able to walk had HDL > 45mg/dl
- Only 3 % of patients who were unable to walk had HDL > 45mg/dl.
- Applying chi square test p < 0.0005 statistically significant.
- This shows patients who had HDL > 45mg/dl had good outcome.

5.3.4 TC/HDL and functional outcome :

Table 5.16 : GLASGOW SCALE REC * TCL / HDL RATIO REC

Crosstab

Count

		TCL / HDL RATIO REC		
		< 4	>4	Total
GLASGOW SCALE REC	DEATH		4	4
	VEG / SEVERE DIS	1	31	32
	MILD/ GOOD	8	8	16
Total		9	43	52

P < 0.0005 (Statistically significant)

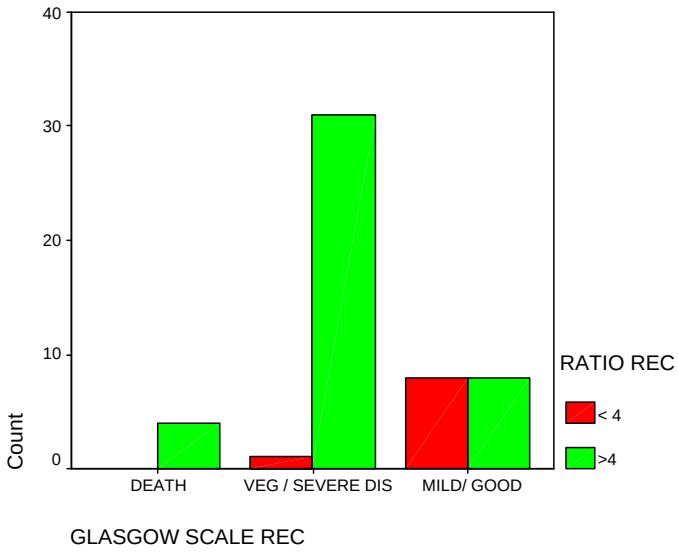

Figure 5.7 : GLASGOW SCALE REC * TCL / HDL RATIO REC

- All the patients who died had TC/HDL > 4.
- 96 % of patients who were unable to walk had TC/HDL > 4.
- Only 50 % of patients who were able to walk had TC/HDL > 4 .
- Applying chi square test p < 0.0005 statistically significant.
- More the TC/HDL, worse the outcome.

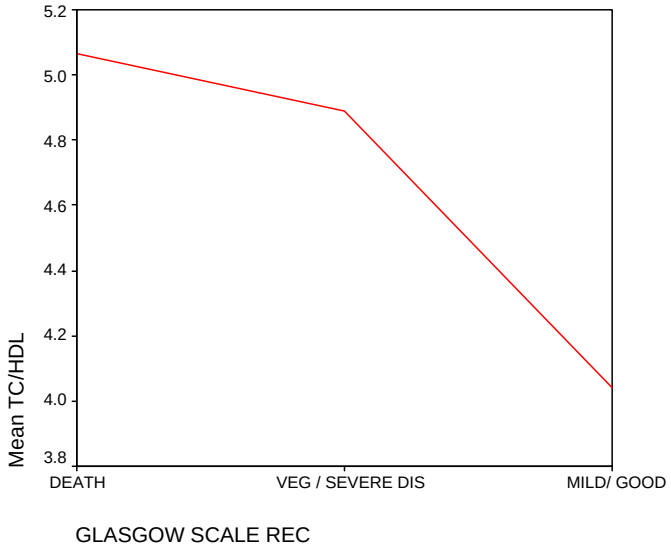

Figure 5.8 : GLASGOW SCALE REC * TCL / HDL RATIO REC(Graph)

- As TC/HDL ratio increases, worse is the outcome

5.3.5 Smoking and functional outcome:

Table 5.17 : GLASGOW SCALE AND SMOKING COMPARISION

Crosstab

Count

		SMOKING		
		YES	NO	Total
GLASGOW SCALE REC	DEATH	3	1	4
	VEG / SEVERE DIS	15	17	32
	MILD/ GOOD	12	4	16
Total		30	22	52

p > 0.05 (NOT SIGNIFICANT)

- Applying chisquare p>0.05, stastistically not significant.
- 75% of patients who died were smokers.

5.3.6 Alcohol and functional outcome:

Table 5.18 : GLASGOW SCALE REC * ALCOHOL COMPARISION

Crosstab

Count

		ALCOHOL		
		YES	NO	Total
GLASGOW SCALE REC	DEATH		4	4
	VEG / SEVERE DIS	6	26	32
	MILD/ GOOD	2	14	16
Total		8	44	52

p > 0.05 (NOT SIGNIFICANT)

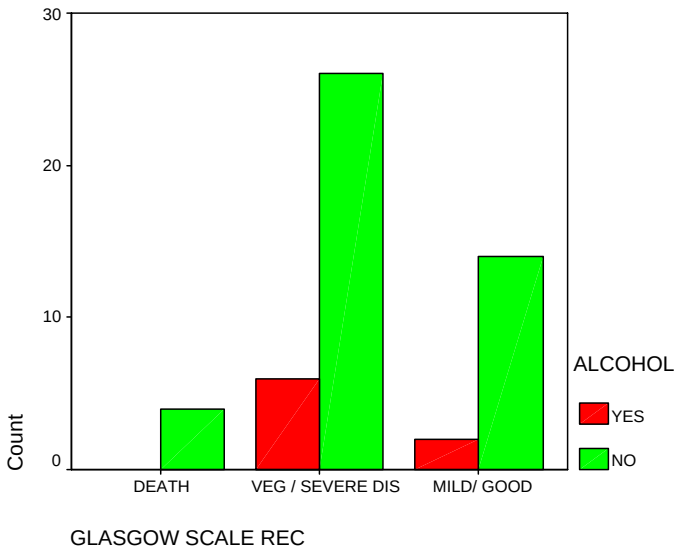

Figure 5.9 : GLASGOW SCALE REC * ALCOHOL COMPARISION

Alcohol not associated with short term outcome in this study.

5.3.7 HT and functional outcome:

Table 5.19 : GLASGOW SCALE REC * H.T

Crosstab

Count

		H.T		
		YES	NO	Total
GLASGOW SCALE REC	DEATH	4		4
	VEG / SEVERE DIS	20	12	32
	MILD/ GOOD	6	10	16
Total		30	22	52

p > 0.05 (NOT SIGNIFICANT)

- Hypertension not associated with short term outcome in this study.

5.3.8 CAHD and functional outcome:

Table 5.20 : GLASGOW SCALE REC * CAHD

Crosstab

Count

		CAHD		
		YES	NO	Total
GLASGOW SCALE REC	DEATH	1	3	4
	VEG / SEVERE DIS	3	29	32
	MILD/ GOOD		16	16
Total		4	48	52

p > 0.05 (NOT SIGNIFICANT)

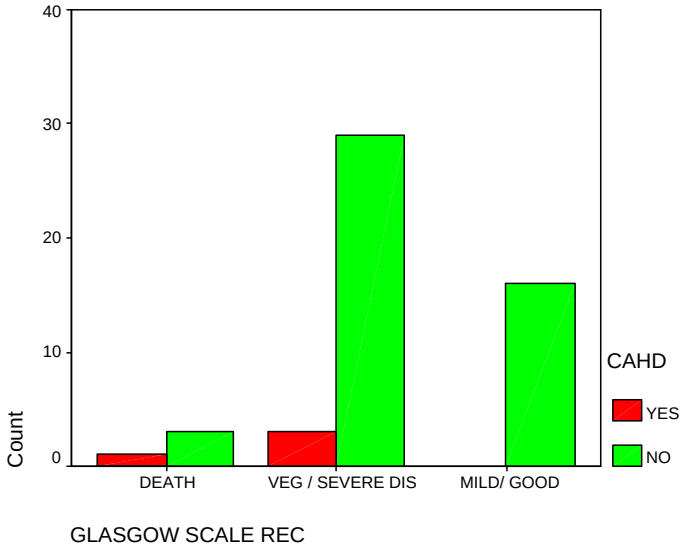

Figure 5.10 : GLASGOW SCALE REC * CAHD

5.3.9 Obesity and functional outcome:

Table 5.21 : GLASGOW SCALE REC * OBESITY

Crosstab

Count

		OBESITY		
		YES	NO	Total
GLASGOW SCALE REC	DEATH	1	3	4
	VEG / SEVERE DIS	4	28	32
	MILD/ GOOD		16	16
Total		5	47	52

p > 0.05 (NOT SIGNIFICANT)

5.3.10 DM and functional outcome:

Table 5.22 : GLASGOW SCALE REC * D.M. COMPARISION

Crosstab

Count

		D.M.		
		YES	NO	Total
GLASGOW SCALE REC	DEATH	2	2	4
	VEG / SEVERE DIS	10	22	32
	MILD/ GOOD		16	16
Total		12	40	52

P = 0.022 (Statistically significant)

Figure 5.11 : GLASGOW SCALE REC * D.M. COMPARISION

- 50% Patients died were alcoholic .
- Applying chi square test p<0.022, statistically significant.
- So diabetes influences outcome in stroke patients**.**

In this study outcome is strongly determined by hs-CRP levels, HDL, TC, TC/HDL levels, and also diabetic status.

5.4 Comparison of Hs CRP with other Known risk factors :

5.4.1 Hs CRP with age:

Mean hs-CRP of all patients: 5.94mg/l.

No of pts in age group 40-50: 10

Mean hs-CRP of pts in age group 40-50: 4.72 mg/l.

No of pts in age group 50-60: 22

Mean hs-CRP of pts in age group 50-60: 5.7 mg/l.

No of pts in age group 60-70: 11

Mean hs-CRP of pts in age group 60-70: 6.56mg/l

No of pts in age group 70-80: 4.

Mean hs-CRP of pts in age group 70-80: 7.12mg/l.

5.4.2 Hs CRP with GENDER:

Mean hs-CRP of all patients: 5.94mg/l.

Mean hs- CRP of men: 5.65mg/l.

Mean hs- CRP of women: 6.38mg/l.

(all are post menopausal)

5.4.3 Hs CRP with SMOKING:

Mean hs- CRP of men: 5.65mg/l.

Mean hs- CRP of men who were smokers: 5.85mg/l.

Mean hs- CRP of men who were non smokers: 5.0 mg/l

5.4.4 Hs CRP with DM:

Mean hs- CRP of pts who were diabetic: 7.73mg/l.

Mean hs- CRP of pts who were non-diabetic: 5.4 mg/l.

5.4.5 Hs CRP with HT:

Mean hs- CRP of pts who were hypertensive: 6.65mg/l.

Mean hs- CRP of pts who were not hypertensive: 4.98mg/l.

5.4.6 Hs CRP with CAHD:

Mean hs- CRP of pts with h/o CAHD: 8.45mg/l.

Mean hs- CRP of pts without h/o CAHD: 5.73mg/l.

5.4.7 Hs CRP with OBESITY:

Mean hs- CRP of pts with BMI>30: 8.18mg/l.

Mean hs- CRP of pts with BMI<30: 5.72 mg/l.

5.4.8 Hs CRP with alcohol:

Mean hs- CRP of pts who were alcoholic: 6.79mg/l.

Mean hs- CRP of pts who were non-alcoholic: 5.79mg/l.

CHAPTER - 6 DISCUSSION

- Discussion

DISCUSSION

Total no of patients in this study was 52. Hs CRP estimate was done on all patients on the second day after the onset of stroke ie, within 24 to 48 hrs after onset of stroke.

Various known risk factors of stroke like age, sex, diabetes, hypertension, smoking, alcohol, total cholesterol level, HDL level, TC/HDL ratio were compared with hs CRP level. Functional outcome after stroke is analysed with hs CRP level and other risk factors.

6.1 AGE:

Of the 52 patients, 10 were in the age group of 40 to 50 yrs, and 22 were in age group of 50 to 60 yrs, 11 were in 60 to 70 yrs and 4 patients were in age group of 70 to 80 yrs.

The mean hs CRP level in each group in ascending order were 4.72mg/l, 5.7mg/l, 6.56mg/l and 7.12mg/l. Thus a gradual increase in hs CRP with age was noted.

This correlates with study by M.A.Mendal et al[41], Praful patel et al, that there is an elevation in hs CRP as age advances. Another study by Seishi yamada et al[77] in Japanese population also confirmed this observation. In the study by Nakogmi et al[1] that in elderly patients there is increase in hs CRP level which in turn increase the production of tissue factor by monocytes. The monocyte tissue factor production is increased by several folds in elderly patients. This tissue factor is responsible for activation of extrinsic coagulation cascade leading to thrombus formation and cardiovascular events in elderly population.

6.2 GENDER:

In this study 39 were male (75 %) and 13 were female (25 %). The mean hs CRP level in male was 5.65mg/l and female was 6.38mg/l.

In a study by Nakagomi et al[1] showed that as age advances the hs CRP level gradually rises. The hs CRP levels of women of post menopausal age were significantly greater than values in men of similar age group. Since all the female patients in this study were postmenopausal the mean hs CRP of females was greater than males.

6.3 SMOKING:

There were 39 men in this study, out of them 30 were smokers who used to smoke greater than 10 cigarettes per day for several years.

Mean hs CRP of the men who smokes was 5.85mg/l and non smokers was 5mg/l.

In a study by Haverkate et al, the elevation of CRP level in smokers is about 50% more than that of non smokers. Study by Timo.E.Strandberg[81] confirmed hs CRP elevation in smokers.

The main mechanism for this elevation may be the increase in inflammation in vessel wall which causes CRP elevation and there by increase in atherosclerosis progression.

In this study there is no strong relationship between smoking and short term prognosis. No study was done previously to find out association between smoking and short term prognosis after stroke.

6.4 ALCOHOL:

Only 8 patients in this study were found to be alcoholic. Mean hs CRP of these patients who were alcoholic and non alcoholic were 6.79mg/l and 5.79mg/l. No study correlates alcohol with hs CRP level.

In this study there is no strong relationship between alcohol intake and short term prognosis. There is no study comparing alcohol with short term prognosis after acute ischemic stroke.

6.5 HYPERTENSION:

♣ HYPERTENSION AND CRP LEVELS:

In this study 30 patients were found to have BP > 140/90 mm Hg at the time of admission. Mean hs CRP level in patients who were hypertensive was 6.65mg/l, whereas the mean hs CRP in non hypertensives was 4.98mg/l.

In a study by Mario Di Napoli et al[14], Franscesca Papa et al[#] and studies by Bautia.L.E, et al, Lopez-Jarmillo et al[#] and studies by Abramson, Weintrub WS et al[#], all showed that there is persistent strong significant association between hs CRP levels and BP. Even high normal BP 130 – 139/ 85 – 89 mm Hg is found to increase CRP levels.

♣ HYPERTENSION AND SHORT TERM OUTCOME:

In this study all the dying patients were found to have high BP, and 63 % of patients who were not able to walk at the end of first week were hypertensive but only 38 % of patients who were able to walk at the end of first week were hypertensive. Though on applying chi square test p value > 0.05 which is not statistically significant.

In the above mentioned studies there is positive correlation between hypertension and long term outcome after stroke, but there is no study that compares hypertension with short term outcome after acute ischemic stroke.

In a study by Benson and Sacco[6], HT confirms relative risk of 3 to 5 fold. HT can result in mechanical injury to endothelium through increased sheer stress, thereby increasing the number of adhesion molecule that attract monocytes and lymphocytes.

6.6 DIABETES:

♣ DIABETES AND HS CRP LEVELS:

In this study 12 patients were found to be diabetic. Mean hs CRP of diabetic patients were 7.7mg/l compared to 5.4mg/l in non diabetics.

In a study by Yudkin et al[32], the elevation of CRP levels in healthy subjects correlates with insulin resistance and endothelial dysfunction. Many studies by Festa.A et al and Leinmoner et al[#] support this. Also study by Manisha Chadalia et al[#] showed that hs CRP concentration in asian Indian living in United States were prone to CVD risk and Diabetes risk.

♣ DIABETES AND SHORT TERM OUTCOME:

50 % of dying patients were diabetic and no diabetic was noted in patients who were able to walk at the end of first week.

Applying chi square test p value is 0.022 which is statistically significant. Previous studies showed that DM increases the risk of stroke and increases the mortality from stroke. Long standing DM is associated with endothelial dysfunction which promotes inflammation[10].DM may be classified as a stroke risk equivalent and may warrant more aggressive treatment strategies in the future prevention of stroke (Hopaultre,Mose 2003[#]).

6.7 CAHD :

♣ CAHD AND HS CRP LEVEL:

In this study of 52 patients, only 4 had previous history of CAHD. Of all the 4 patients one died during the study and the other 3 are with severe disability / vegetative state.

Mean hs CRP of patients with previous history of CAHD is 8.45mg/l. Mean hs CRP of patients without previous history of CAHD is 5.73mg/l.

♣ CAHD AND FUNCTIONAL OUTCOME:

On applying chi square test p value is > than 0.05 statistically not significant. Studies by Kerstein Weinbeck et al[34], has found out CRP levels after 12 hours of any cardiovascular event predicts the outcome and risk of recurrent events.

6.8 OBESITY:

♣ OBESITY AND HS CRP LEVELS:

Mean hs CRP of patients who have BMI > 30 in our study were 8.18mg/l, where as mean hs CRP of patients who have BMI < 30 were 5.72mg/l. In this study only 5 were found to be obese.

This study strongly correlates with previous study by Yudkin et al[32] that hs CRP elevation in obesity is due to release of IL-6 from adipose tissue that stimulate the hepatic production of CRP leading to increased CRP levels. Similar study by Haverkate et al[#] confirmed this observation.

♣ OBESITY AND FUNCTIONAL OUTCOME:

Though studies support obesity with long term poor outcome after stroke there is no study to find out association between obesity and short term outcome after stroke. In this study on applying chi square test to find out association between obesity and short term outcome p value > 0.05 statistically not significant.

6.9 TOTAL CHOLESTEROL AND FUNCTIONAL OUTCOME:

In this study 37 patients had total cholesterol < 200mg/dl. 75 % of people who died during study had a TC > 200mg/dl. 34 % of people who were unable to walk after one week had TC > 200mg/dl. Only 6 % of patients who were able to walk after one week had a TC > 200mg/dl.

On applying chi square test to find out association between TC and short term outcome after stroke, p value is 0.014 which is statistically significant. This was supported by many studies.

"Benzafibrate" prevention by Nirokiren Morag et al and Sacco et al[47], showed that patients with high TC had poor outcome.

6.10 HDL LEVEL AND FUNCTIONAL OUTCOME:

In this study only 11 patients had HDL level > 45mg/dl and 41 patients had HDL level < 45mg/dl.

56 % of patients who were able to walk at the end of first week had HDL > 45mg/dl but only 25 % of patients who died during study had HDL > 45mg/dl. Only 3 % of patients who were unable to walk at the end of first week had HDL > 45mg/dl.

On applying chi square test $p < 0.0005$, which is highly significant. Patients who had HDL > 45mg/dl had better outcome. This was supported by many studies. "Benzafibrate" prevention by Nirokiren Morag et al and Sacco et al[47], showed that patients with low HDL had poor outcome.

In the study by Russel P. Tracy Rozenn, N.Lemaitre et al[83]., the levels of hs CRP correlated proportionately with LDL level and inversely with HDL level. This proves the role of inflammation on LDL – C for the progression of atherosclerosis.

6.11 TC / HDL RATIO AND FUNCTIONAL OUTCOME

In this study totally 43 patients had TC/HDL > 4, all the dying patients had TC/HDL >4. 96 % of patients with Glasgow outcome scale score of 2 & 3 had TC/HDL > 4. Only 50 % of patients with GOS score of 4 & 5 had TC/HDL > 4.

On applying chi square test to find out association between TC/HDL ratio with GOS score, p value is < 0.0005, which is statistically significant. Studies by Bruce Kinosian et al[#], showed that TC/HDL is a superior measure of cardiovascular disease compared with either with TC or LDL-C.

The addition of CRP to other CVD risk factors increased the over all predictive value. In particular when hs CRP & TC/HDL ratio were used together a significant improvement in risk assessment was achieved compared to use of each separately (Ridiker).

6.12 Hs CRP LEVEL AND FUNCTIONALOUTCOME:

In this study of 52 patients the mean hs CRP of all patients done on 2nd day after onset of stroke was 5.94 ± 1.96 mg/l.

Mean hs CRP of patients who had death as end point was 8.85 ± 1.98 mg/l.

Mean hs CRP of patients who had Glasgow outcome scale score of 2 & 3 (patients unable to walk) at the end of 1st week was 6.68 ± 1.1 mg/l.

Mean hs CRP of patients who had Glasgow outcome scale score of 4 & 5 (patients able to walk) at the end of 1st week was 3.73 ± 1.1 mg/l.

Mean hs CRP of patients who had massive infarct in CT Brain was 8.7 ± 0.96 mg/l, whereas mean hs CRP of patients who had lacunar infarct was 3.27 ± 0.93 mg/l.

All these datas clearly show that hs CRP is increased after stroke and the patients who had poor outcome at the end of 1st week after stroke had very high levels of hs CRP

When we apply chi square test for association between hs CRP levels and Glasgow outcome scale for our patients p value is < 0.0005, which is statistically significant.

Studies by Tahir Yoldas et al[80] (mediators of inflammation 2007), clearly showed that levels of hs CRP done on 2nd day after the ischemic stroke strongly associated with short term unfavorable prognosis. The study also showed that patients with stroke have a higher circulating serum hs CRP and Homocysteine levels.

Studies by Kerstein Weinbeck et al[34] (stroke 2002) also gave similar results. Beamer et al[#] have reported that stroke patients without infections have increased levels of CRP.

Experimental studies have shown that secretion of inflammatory mediators as a direct response to cerebral injury starts within 2 hours of focal ischemia and anti inflammatory treatment have neuroprotective role.

Muir et al[44], have shown CRP levels within 1st 72 hours following an acute ischemic stroke as an independent predictor for predicting survival.

Studies by Di Napoli[14] has shown that a large infarct and cortical involvement in patients had a highest CRP values than normal at the time of presentation. This study also confirmed that prognosis in patients with increased CRP level is worse.

Our findings that patients who were able to walk had lower hs CRP levels than the patients who were unable to walk, and also the patients who had death as end point, may be an indicator of the degree of inflammation.

CARE Trial, PROVE-IT-TIMI[51] (PROVASTATIN or ATORVASTATIN evaluation and infection therapy – thrombolysis in myocardial infarction), and REVERSAL (Reversing atherosclerosis with aggressive lipid lowering trials), showed that STATINS significantly reduce mortality and recurrent events in patients with high hs CRP levels even when LDL levels are < 130 mg/dl.

CHAPTER – 7 SUMMARY & CONCLUSION

- Conclusion

Summary and conclusion

1. The hs CRP level is increased in all patients after acute ischemic stroke.
2. The hs CRP level strongly correlates with short term outcome in patients after first ever ischemic stroke. ($p < 0.0005$)
3. The hs CRP level is high in patients with massive infarct thus reflecting the severity of stroke.
4. The hs CRP level is increased in smokers, obesity, diabetes, hypertension and post menopausal women.
5. The hs CRP level increases as age advances.
6. TC/HDL ratio,HDL level (<45mg/dl) strongly correlate with short term outcome after acute ischemic stroke. ($p < 0.0005$)
7. TC level (>200mg/dl),diabetic status(FBS>125mg/dl), strongly correlate with short term out come after acute ischemic stroke.($p=0.022$)

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APPENDIX

- A: Proforma
- B: Master chart

PROFORMA

Name:..... Age:..... yrs Sex: M/F

IP No:..... Ward:..... Unit:

Presenting Complaints:

Weakness ☐ Loss of consciousness ☐ Facial Weakness ☐

Speech disturbance ☐ Others ☐

Risk Factors:

Diabetes Mellitus ☐ Hypertension ☐ CAHD ☐

Smoking ☐ Alcohol ☐ Hyperlipidemia ☐ Obesity ☐

Clinical Examination:

CNS: Conscious: yes/no

Orientation: yes/no

Speech: Normal/Aphasia/Dysphasia

UMN Facial Palsy: yes/no

Motor System: Hemiplegia/Hemiparesis/Monoplegia/ Monoparesis/Others

Others:

CVS:

RS:

ABDOMEN:

BMI: ☐ >30 ☐ <30

Investigations:

URINE:

Albumin: Sugar: Deposit:

COMPLETE HEMOGRAM:

Hb: TC: DC: P % L % E % B % M %
RBC:
Platelets:

BIOCHEMICAL ANALYSIS:

Blood Sugar:
Blood Urea:
Serum Creatinine:
Serum Electrolytes: Na^+ K^+

LIPID PROFILE:

Total Cholesterol:
HDL:
TC/HDL Ratio:

ECG:

High sensitivity CRP:
(on 2nd day of stroke)

CT BRAIN:

FUNCTIONAL OUTCOME:
(on 7th day of stroke)

Glasgow outcome scale score: 1 / 2 / 3 / 4 / 5

MASTER CHART

S.No.	Name	AGE	SEX	IP.No	RISK FACTORS						INVESTIGATIONS					On 2nd Day	At Discharge
					Smoking	Alcohol	DM	HT	IHD	OBESITY	Blood sugar mg	TC Mg %	HDL Mg %	TC / HDL	CT Brain Plain	HS CRP Mg / L	Glasgow Outcome Scale (Score)
1	Pappathi	55	F	941880	-	-	-	+	-	-	98	196	44	4.45	(R) MCA Infarct	6.8	3
2	Maideen Beevi	45	F	942712	-	-	+	+	-	+	226	208	41	5.07	(L) MCA Infarct	7.0	3
3	Saudambal	70	M	922704	-	-	-	+	-	-	101	190	45	4.22	(L) MCA Infarct	7.1	3
4	Karunanidhi	60	M	929370	+	+	-	+	+	-	88	201	36	5.59	(L) Hemispherical Massive Infarct	9.1	2
5	Jeganathan	80	M	929921	-	-	-	+	-	-	92	184	36	5.10	(L) MCA Infarct	6.9	3
6	Samson	45	M	930175	+	-	-	+	-	-	84	190	45	4.22	(R) MCA Infarct	3.1	4
7	Lakshmi	58	F	932265	-	-	-	-	-	-	89	195	39	5.00	(L) Capsuloganglionic Infarct	4.2	3
8	Chinnathambi	60	M	931912	-	-	-	-	-	-	84	181	42	4.30	(L) Subcortical Infarct	3.0	4
9	Rajammal	80	F	934927	-	-	-	+	-	-	109	192	43	4.50	® MCA Massive Infarct	9.8	1
10	Kasthuri	60	F	943133	-	-	+	-	-	+	301	209	40	5.23	(L) Massive Infarct + ® Frontal Infarct	8.1 Mg	2

S.No.	Name	AGE	SEX	IP.No	RISK FACTORS						INVESTIGATIONS					On 2nd Day	At Discharge
					Smoking	Alcohol	DM	HT	IHD	OBESITY	Blood sugar mg	TC Mg %	HDL Mg %	TC / HDL	CT Brain Plain	HS CRP Mg / L	Glasgow Outcome Scale (Score)
11	Anjalai	61	F	955243	-	-	-	-	-	-	78	170	45	3.78	®Sub cortical Infarct	2.1	5
12	Karunanidhi	60	F	941656	-	-	-	-	-	-	88	168	42	4.00	(L) ACA Infarct	6.2	3
13	Maideen	55	F	912441	-	-	-	+	-	-	99	201	46	4.37	(R) Parietal Infarct	4.9	4
14	Ashokan	44	M	931905	+	+	+	+	+	+	304	198	38	5.21	(L) MCA Infarct	7.5	3
15	Chinnaiyan	59	M	925233	+	+	-	-	+	-	98	210	37	5.67	(L) MCA Infarct	7.6	3
16	Kanagaraj	57	M	933599	+	-	-	+	-	-	79	188	36	5.22	(R) MCA Infarct	6.9	3
17	Thangarajan	75	M	933601	+	-	-	+	-	-	88	174	40	4.35	(R) MCA Infarct	5.8	3
18	Kandhan	75	M	933329	-	-	-	-	-	-	101	196	42	4.66	(R) CapsuloganglionicInfarct	5.4	3
19	Arokiasamy	45	M	935306	+	+	-	-	-	-	120	186	45	4.13	(L)Sub cortical Infarct	2.9	4
20	Vellangani	65	M	935178	+	-	+	+	-	-	292	211	41	5.14	(L)MCA Massive Infarct	8.0	2
21	Chinnakanu	75	M	935338	+	-	-	-	-	-	113	168	40	4.20	(R) MCA Infarct	6.0	3
22	Rengasamy	70	M	936125	+	-	-	+	-	-	98	190	44	4.31	(R)MCA Massive Infarct	7.4	2

S.No.	Name	AGE	SEX	IP.No	RISK FACTORS						INVESTIGATIONS					On 2nd Day	At Discharge
					Smoking	Alcohol	DM	HT	IHD	OBESITY	Blood sugar mg	TC Mg %	HDL Mg %	TC / HDL	CT Brain Plain	HS CRP Mg / L	Glasgow Outcome Scale (Score)
23	Natarajan	52	M	938218	+	-	-	-	-	-	96	160	45	3.50	® Lacunar Infarct	2.4	5
24	Taichuddin	67	M	936112	+	-	+	+	-	+	284	214	37	5.70	(R)MCA Massive Infarct	10.1	1
25	Rengasamy	75	M	938714	-	-	-	+	-	-	94	168	35	4.80	(L)MCA Infarct	6.9	3
26	Rajagopalan	45	M	934137	+	-	-	-	-	-	92	180	42	4.29	(L) Parietal Infarct	3.8	4
27	Ramalingam	56	M	924258	-	-	-	+	-	-	84	168	44	3.81	(R) MCA Infarct	4.5	4
28	Palanisamy	60	M	941154	+	-	-	-	-	-	82	190	43	4.41	(L)MCA Infarct	6.6	3
29	Raman	70	M	941659	+	+	-	-	-	-	97	178	39	4.56	(R) MCA Infarct	7.2	3
30	Marudhamuthu	60	M	941625	+	-	-	+	-	-	93	156	37	4.22	(L)MCA Infarct	6.8	3
31	Natesan	69	M	941664	-	-	-	+	-	-	89	181	38	4.76	(L)MCA Infarct	6.7	3
32	Subramanian	55	M	941859	+	-	-	-	-	-	98	162	42	3.86	(L)Sub cortical Infarct	4.4	4
33	Sadhasivam	70	M	912308	+	-	+	-	-	-	199	204	38	5.37	(L)MCA Infarct	6.7	3
34	Ramachandran	43	M	942718	+	-	-	-	-	-	86	182	46	3.96	(R)Sub cortical Infarct	3.8	4

S.No.	Name	AGE	SEX	IP.No	RISK FACTORS						INVESTIGATIONS					On 2nd Day	At Discharge
					Smoking	Alcohol	DM	HT	IHD	OBESITY	Blood sugar mg	TC Mg %	HDL Mg %	TC / HDL	CT Brain Plain	HS CRP Mg / L	Glasgow Outcome Scale (Score)
35	Chinaiyan	75	M	942691	+	+	+	+	-	-	324	216	37	5.84	(L)MCA Massive Infarct	8.0	2
36	Kaliyamoorthi	60	M	945274	-	-	-	+	-	-	95	196	41	4.78	(L) CapsuloganglionicInfarct	5.5	3
37	Rajangam	45	M	945275	+	-	-	-	-	-	88	172	42	4.09	(R) Parietal Infarct	5.6	4
38	Gopalakrishnan	51	M	946712	-	-	+	-	-	-	248	188	37	5.08	(L)MCA Infarct	6.1	3
39	Appadurai	48	M	948367	+	-	-	-	-	-	89	160	45	3.56	® Lacunar Infarct	2.4	5
40	Swamy Nathan	54	M	950133	+	-	+	+	+	-	314	211	39	5.40	(L)MCA Massive Infarct	9.6	1
41	Anthony Samy	64	M	950715	-	-	-	+	-	-	97	200	41	4.88	(R) Capsuloganglionic Infarct	5.4	3
42	Savithiri	63	F	950980	-	-	-	+	-	-	88	210	42	5.00	(R) MCA Infarct	4.8	3
43	Paavai	70	F	954330	-	-	+	+	-	-	284	212	40	5.30	(L)MCA Infarct	6.6	3
44	Marriammal	78	F	951306	-	-	-	+	-	-	92	200	38	5.26	(L)MCA Infarct	7.1	3
45	Poongodhai	76	F	954310	-	-	+	+	-	+	311	210	40	5.25	(R)MCA Massive Infarct	8.2	2
46	Murugaiyan	50	F	954335	+	-	-	-	-	-	89	190	41	4.63	B/L Occipital Infact	4.2	3

S.No.	Name	AGE	SEX	IP.No	RISK FACTORS						INVESTIGATIONS					On 2nd Day	At Discharge
					Smoking	Alcohol	DM	HT	IHD	OBESITY	Blood sugar mg	TC Mg %	HDL Mg %	TC / HDL	CT Brain Plain	HS CRP Mg / L	Glasgow Outcome Scale (Score)
47	Thangaiyan	55	M	954316	+	-	-	-	-	-	88	200	45	4.44	(R)Sub cortical Infarct	3.9	5
48	Gnanasundram	55	M	955286	+	-	-	+	-	-	86	210	45	4.67	Brain Stem Infarct	5.9	1
49	Kuppusamy	60	M	955612	+	+	-	+	-	-	97	200	42	4.76	(L) Cerebellar Infarct	5.1	4
50	Sivakozhundhu	51	M	947202	+	-	-	+	-	-	104	164	42	3.90	® Lacunar Infarct	2.9	5
51	Rayar	50	M	947181	+	+	+	-	-	-	401	204	41	4.98	(L)MCA Infarct	6.9	3
52	Lakshmanan	55	M	954710	+	-	-	+	-	-	92	168	45	3.73	(L)Sub cortical Infarct	4.9	4